Soluble amyloid precursor protein induces rapid neural differentiation of human embryonic stem cells.

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Public Summary:

Scientific Abstract:
Human embryonic stem cells (hESCs) offer tremendous potential for not only treating neurological disorders but also for their ability to serve as vital reagents to model and investigate human disease. To further our understanding of a key protein involved in Alzheimer disease pathogenesis, we stably overexpressesed amyloid precursor protein (APP) in hESCs. Remarkably, we found that APP overexpression in hESCs cells caused a rapid and robust differentiation of pluripotent stem cells towards a neural fate. Despite maintenance in standard hES cell media, up to 80% of cells expressed the neural stem cell marker nestin and 65% exhibited the more mature neural marker TUJ within just 5 days of passaging. To elucidate the mechanism underlying the effects of APP on neural differentiation, we examined the proteolysis of APP and performed both gain-of-function and loss-of-function experiments. Taken together, our results demonstrate that N-terminal secreted soluble forms of APP (in particular sAPPbeta) robustly drive neural differentiation of hESCs. Our findings not only reveal a novel and intriguing role for APP in neural lineage commitment but also identify a straightforward and rapid approach to generate large numbers of neurons from human embryonic stem cells. These novel APP-hES cell lines represent a valuable tool to investigate the potential role of APP in development, neurodegeneration and allow for insights into physiological functions of this protein.